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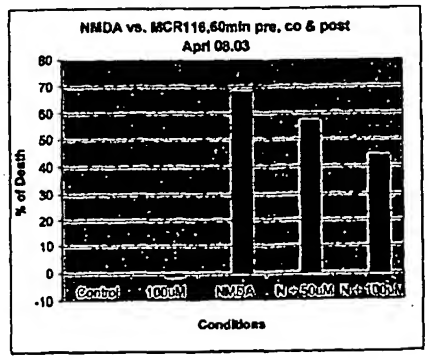
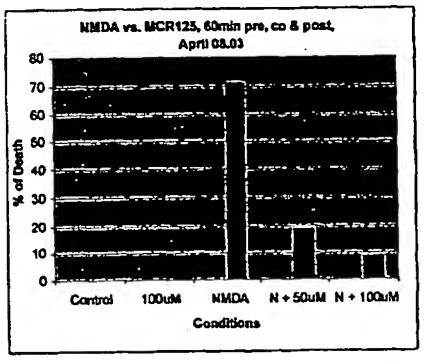
(54) Title: AMINO BENZOTHIAZOLE COMPOUNDS WITH NOS INHIBITORY ACTIVITY





(57) Abstract: The present invention provides novel amino benzothiazole compounds, compositions comprising these compounds and methods of using these compounds as neuroprotectants. In particular, the compounds described in the present invention are useful for treating stroke.

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AMENDED CLAIMS
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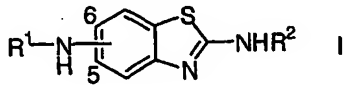
Claim 1-37 relaced by claims 1-37.

WE CLAIM:

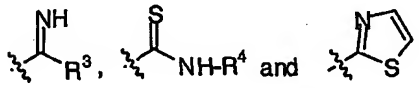
1. A compound of Formula I, and pharmaceutically acceptable salts, hydrates, solvates and prodrugs thereof:



I

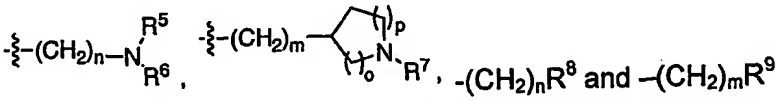
wherein

R^1 is selected from the group consisting of:



;

R^2 is selected from the group consisting of H,



$-(CH_2)_nR^8$ and $-(CH_2)_mR^9$

R^3 is selected from the group consisting of C_{1-6}alkyl, SC_{1-6}alkyl, thienyl and furanyl;

R^4 is selected from the group consisting of H, C_{1-6}alkyl, Ph, C(O)Ph and $-C(O)C_{1-6}$alkyl;

R^5 and R^6 are independently selected from the group consisting of H and C_{1-6}alkyl or together R^5 and R^6 and the nitrogen to which they are attached form a 3 to 7-membered azacarbocylic ring wherein one of the carbon atoms in the ring may optionally be replaced with O, S, or NR^7;

R^7 is selected from the group consisting of H, C_{1-6}alkyl, Ph, Heteroaryl, CH_2Ph, and CH_2Heteroaryl, with Ph and Heteroaryl being optionally substituted with 1-3 groups independently selected from the group consisting of C_{1-4}alkyl, halo, OH, OC_{1-4}alkyl, NH_2, $NH(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)(C_{1-4}alkyl)$, nitro and cyano;

R^8 is selected from the group consisting of H, OH, Ph, naphthyl and heteroaryl, with Ph, naphthyl and heteroaryl being optionally substituted with 1-3 groups independently selected from the group consisting of C_{1-4}alkyl, halo, NH_2, $NH(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)(C_{1-4}alkyl)$, nitro, cyano, OH and OC_{1-4}alkyl;

R^9 is C_{3-7}cycloalkyl optionally substituted with 1-3 groups independently selected from the group consisting of C_{1-4}alkyl, halo, NH_2, $NH(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)(C_{1-4}alkyl)$, nitro, cyano, OH and OC_{1-4}alkyl and one or two of the carbon atoms in C_{3-7}cycloalkyl may optionally be replaced with O or S;

n is 1-6;

m is 0-6;

o is 0-2;

p is 1-2; and

the group R^1NH- is attached to the 5- or 6-position of the aminobenzothiazole ring, with the proviso that when R^2 is H then R^4 is not C_{1-6}alkyl.

2. The compound according to claim 1, wherein R^3 is selected from the group consisting of C_{1-2}alkyl, SC_{1-4}alkyl and thienyl.

3. The compound according to claim 2, wherein R^3 is selected from the group consisting of SC_{1-2}alkyl and thienyl.

4. The compound according to any one of claims 1-3, wherein R^4 is selected from the group consisting of H, C_{1-4}alkyl, Ph, C(O)Ph and -$C(O)C_{1-4}$alkyl.

5. The compound according to claim 4, wherein R^4 is selected from the group consisting of H, and C(O)Ph.

6. The compound according to any one of claims 1-5, wherein R^5 and R^6 are independently selected from a group consisting of H and C_{1-4}alkyl or together R^5 and R^6 and the nitrogen to which they are attached form a 4 to 6-membered azacarbocylic ring wherein one of the carbon atoms in the ring may optionally be replaced with O, S, or NR^7.

7. The compound according to claim 6, wherein R^5 and R^6 are independently selected from a group consisting of H and CH_3 or together R^5

and R^6 and the nitrogen to which they are attached form a 5 to 6-membered azacarbocylic ring.

8. The compound according to any one of claims 1-7, wherein R^7 is selected from H, C_{1-4}alkyl, Ph, Heteroaryl, CH_2Ph, and CH_2Heteroaryl, with Ph and Heteroaryl being optionally substituted with 1-2 groups independently selected from the group consisting of C_{1-4}alkyl, halo, OH, OC_{1-4}alkyl, NH_2, $NH(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)(C_{1-4}alkyl)$, nitro and cyano.

9. The compound according to claim 8, wherein R^7 is selected from H, C_{1-4}alkyl, Ph, Heteroaryl, CH_2Ph, and CH_2Heteroaryl, with Ph and Heteroaryl being optionally substituted with 1 group independently selected from the group consisting of C_{1-4}alkyl, halo, OH, OC_{1-4}alkyl, NH_2, $NH(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)(C_{1-4}alkyl)$, nitro and cyano.

10. The compound according to claim 9, wherein R^7 is selected from H, Ph, C_{1-4}alkyl and CH_2Ph, with Ph being optionally substituted with 1 groups independently selected from the group consisting of C_{1-4}alkyl, halo, OH, OC_{1-4}alkyl, NH_2, $NH(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)(C_{1-4}alkyl)$, nitro and cyano.

11. The compound according to claim 10, wherein R^7 is selected from H, C_{1-2}alkyl, Ph and CH_2Ph, with Ph being optionally substituted with 1 groups independently selected from the group consisting of methyl, halo, OH, methoxy, NH_2, NHMe, NMe_2 nitro and cyano.

12. The compound according to claim 11, wherein R^7 is selected from methyl and CH_2Ph.

13. The compound according to any one of claims 1-12, wherein R^8 is selected from the group consisting of H, OH, Ph and heteroaryl, with Ph and heteroaryl being optionally substituted with 1-2 groups independently selected

from the group consisting of C_{1-4}alkyl, halo, NH_2, $NH(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)(C_{1-4}alkyl)$, nitro, cyano, OH and OC_{1-4}alkyl.

14. The compound according to claim 13, wherein R^8 is selected from the group consisting of H, OH, Ph, and heteroaryl, with Ph and heteroaryl being optionally substituted with 1 group independently selected from the group consisting of C_{1-4}alkyl, halo, NH_2, $NH(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)(C_{1-4}alkyl)$, nitro, cyano, OH and OC_{1-4}alkyl.

15. The compound according to any one of claims 13-14 wherein heteroaryl is a 5 or 6 membered aromatic ring.

16. The compound according to claim 15, wherein heteroaryl is selected from pyridyl, imidazolyl, thienyl and furanyl.

17. The compound according to any one of claims 1-16, wherein R^9 is C_{3-7}cycloalkyl optionally substituted with 1-2 groups independently selected from the group consisting of C_{1-4}alkyl, halo, NH_2, $NH(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)(C_{1-4}alkyl)$, nitro, cyano, OH and OC_{1-4}alkyl and wherein one of the carbon atoms in C_{3-7}cycloalkyl may optionally be replaced with O or S.

18. The compound according to claim 17, wherein R^9 is C_{5-7}cycloalkyl optionally substituted with 1 group independently selected from the group consisting of C_{1-4}alkyl, halo, NH_2, $NH(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)(C_{1-4}alkyl)$, nitro, cyano, OH and OC_{1-4}alkyl and wherein one of the carbon atoms in C_{3-7}cycloalkyl may optionally be replaced with O or S.

19. The compound according to claim 18, wherein R^9 is C_{5-7}cycloalkyl herein one of the carbon atoms in C_{3-7}cycloalkyl may optionally be replaced with O.

20. The compound according to claim 17, wherein R^9 is selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, tetrahydropyranyl and tetrahydrofuran.

21. The compound according to any one of claims 1-20, n is 1-4.

22. The compound according to claim 21, wherein n is 2.

23. The compound according to any one of claims 1-22, wherein m is 0-2.

24. The compound according to claim 23, wherein m is 0.

25. The compound according to any one of claims 1-24, wherein both o and p are 1 (to provide a pyrrolidinyl ring).

26. The compound according to any one of claims 1-24, wherein both o and p are 2 (to provide a piperidinyl ring).

27. The compound according to any one of claims 1-26, wherein R^1 is  .

28. The compound according to any one of claims 1-26, wherein R^1 is  .

29. The compound according to claim 1 that is selected from the group consisting of:

N-(2-Amino-benzothiazol-6-yl)-2-methylthiocarboximidamide;

N-(2-Amino-benzothiazol-6-yl)-2-ethylthiocarboximidamide;

N-(2-Amino-benzothiazol-6-yl)-2-propylthiocarboximidamide;

N-(2-Amino-benzothiazol-6-yl)-2-isopropylthiocarboximidamide;

N-(2-Amino-benzothiazol-6-yl)-2-methylcarboximidamide;
N-(2-Amino-benzothiazol-6-yl)-2-thiophenecarboximidamide;
N-[2-(2-pyrrolidin-1-ylethylamino)-benzothiazol-6-yl]-2-thiophenecarboximidamide;
1-(2-Amino-benzothiazol-5-yl)-3-benzoyl-thiourea;
1-(2-Amino-benzothiazol-5-yl)-3-ethyl-thiourea;
N-(2-Amino-benzothiazol-5-yl)-thiophene-2-carboxamidine;
N5-Thiazol-2-yl-benzothiazole-2,5-diamine;
(2-Amino-benzothiazol-5-yl)-thiourea;
N-[2-(Tetrahydro-pyran-4-ylamino)-benzothiazol-6-yl]-thiophene-2-carboxamidine;
N-{2-[2-(4-Bromo-phenyl)-ethylamino]-benzothiazol-6-yl}-thiophene-2-carboxamidine;
N-[2-(2-Pyridin-2-yl-ethylamino)-benzothiazol-6-yl]-thiophene-2-carboxamidine;
N-[2-(1-Benzyl-piperidin-4-ylamino)-benzothiazol-6-yl]-thiophene-2-carboxamidine;
N-{2-[2-(3H-Imidazol-4-yl)-ethylamino]-benzothiazol-6-yl}-thiophene-2-carboxamidine;
N-[2-(2-Morpholin-4-yl-ethylamino)-benzothiazol-6-yl]-thiophene-2-carboxamidine;
N-[2-(2-Dimethylamino-ethylamino)-benzothiazol-6-yl]-thiophene-2-carboxamidine;
N-{2-[2-(1-Methyl-pyrrolidin-2-yl)-ethylamino]-benzothiazol-6-yl}-thiophene-2-carboxamidine;
N-{2-[2-(3-Chloro-phenyl)-ethylamino]-benzothiazol-6-yl}-thiophene-2-carboxamidine;
N-[2-(4-Hydroxy-butylamino)-benzothiazol-6-yl]-thiophene-2-carboxamidine;
N-[2-(3-Imidazol-1-yl-propylamino)-benzothiazol-6-yl]-thiophene-2-carboxamidine;
N2-(1-Benzyl-piperidin-4-yl)-N6-thiazol-2-yl-benzothiazole-2,6-diamine;
1-Benzoyl-3-{2-[2-(4-bromo-phenyl)-ethylamino]-benzothiazol-6-yl}-thiourea;

{2-[2-(4-Bromo-phenyl)-ethylamino]-benzothiazol-6-yl}-thiourea; and 1-{2-[2-(4-Bromo-phenyl)-ethylamino]-benzothiazol-6-yl}-2-ethyl-isothiourea.

30. A pharmaceutical composition comprising a compound according to any of claims 1-29 and a pharmaceutically acceptable carrier.

31. A method of treating, or reducing the risk of, a disease or condition which benefits from an inhibition of NOS activity comprising administering an effective amount of a compound according to any one of claims 1-29, including those where R^2 is H and R^4 is C_{1-6}alkyl, to a cell or animal in need thereof.

32. A use of a compound according to any one of claims 1-29, including those where R^2 is H and R^4 is C_{1-6}alkyl, to treat, or reduce the risk of, a disease or condition which benefits from an inhibition of NOS activity.

33. A use of a compound according to any one of claims 1-29, including those where R^2 is H and R^4 is C_{1-6}alkyl, to prepare a medicament to treat, or reduce the risk of, a disease or condition which benefits from an inhibition of NOS activity.

34. The method according to claim 31, wherein the disease or condition that may benefit from an inhibition of NOS activity is selected from the group consisting of migraine, inflammatory diseases including reversible obstructive airway diseases (e.g., asthma and adult respiratory distress syndrome (ARDS)), stroke, neurological deficits associated with coronary artery bypass graft (CABG), acute and chronic pain, neuropathic pain, traumatic shock, reperfusion injury, multiple sclerosis, AIDS associated dementia, neurodegenerative diseases, neuron toxicity, Alzheimer's disease, chemical dependencies and addictions (e.g., dependencies on drugs, alcohol and nicotine), epilepsy, anxiety, head trauma, morphine induced tolerance and

withdrawal symptoms, acute spinal cord injury, Huntington's disease, Parkinson's disease, glaucoma, macular degeneration, diabetic nephropathy.

35. The method according to claim 34, wherein the disease or condition that may benefit from an inhibition of NOS activity is selected from the group consisting of stroke, reperfusion injury, neurodegeneration, head trauma, neurological deficits associated with CABG, migraine, neuropathic pain and chronic pain.

36. The use according to claim 32 or 33 wherein the disease or condition that may benefit from an inhibition of NOS activity is selected from the group consisting of migraine, inflammatory diseases including reversible obstructive airway diseases (e.g., asthma and adult respiratory distress syndrome (ARDS)), stroke, neurological deficits associated with coronary artery bypass graft (CABG), acute and chronic pain, neuropathic pain, traumatic shock, reperfusion injury, multiple sclerosis, AIDS associated dementia, neurodegenerative diseases, neuron toxicity, Alzheimer's disease, chemical dependencies and addictions (e.g., dependencies on drugs, alcohol and nicotine), epilepsy, anxiety, head trauma, morphine induced tolerance and withdrawal symptoms, acute spinal cord injury, Huntington's disease, Parkinson's disease, glaucoma, macular degeneration, diabetic nephropathy.

37. The use according to claim 36, wherein the disease or condition that may benefit from an inhibition of NOS activity is selected from the group consisting of stroke, reperfusion injury, neurodegeneration, head trauma, neurological deficits associated with CABG, migraine, neuropathic pain and chronic pain.